

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



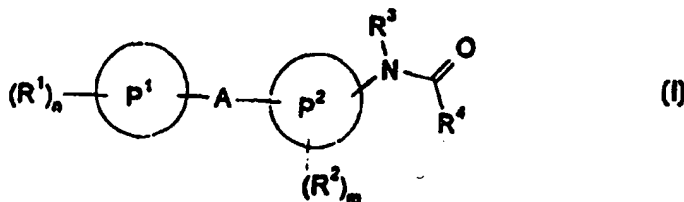
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : C07D 401/12, A61K 31/44, C07D 401/14		A1	(11) International Publication Number: WO 97/37989
			(43) International Publication Date: 16 October 1997 (16.10.97)
(21) International Application Number: PCT/EP97/01611		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 26 March 1997 (26.03.97)		Published With international search report.	
(30) Priority Data: 9607219.4      4 April 1996 (04.04.96)      GB			
(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).			
(72) Inventor; and			
(75) Inventor/Applicant (for US only): BROMIDGE, Steven, Mark [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).			
(74) Agent: WATERS, David, Martin; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).			

(54) Title: INDOLE DERIVATIVES AS 5-HT RECEPTOR ANTAGONIST

(57) Abstract

Prodrugs of 5HT<sub>2c</sub> receptor antagonists of formula (I) wherein the prodrug has a quaternary ammonium group, in particular a quaternary pyridinium group.



BEST AVAILABLE COPY

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## INDOLE DERIVATIVES AS 5-HT RECEPTOR ANTAGONIST

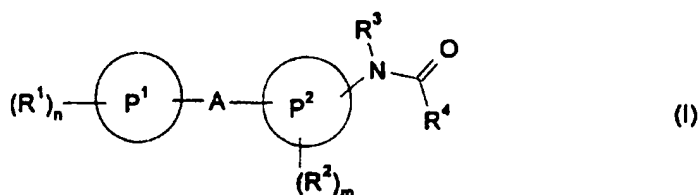
This invention relates to compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

Compounds having 5HT<sub>2C</sub> receptor antagonist activity are known in the art. For example PCT/EP96/00368 discloses indoline derivatives as 5HT<sub>2C</sub> antagonists.

However certain 5HT<sub>2C</sub> receptor antagonists exhibit poor solubility which may lead to decreased activity. It has now been found that pyridinium derivatives of certain known 5HT<sub>2C</sub> receptor antagonists show increased solubility and increased *in vivo* activity. It is believed that these new compounds are converted to their 'parent' compounds prior/during/or after absorption and so may increase the bioavailability of the 'parent' compound. The compounds of the invention may therefore act as prodrugs and are defined as prodrugs herein.

The present invention therefore provides, in a first aspect, a prodrug of a 5HT<sub>2C</sub> receptor antagonist wherein the prodrug has a quaternary ammonium group, in particular a quaternary pyridinium group.

Preferably the invention provides a compound of formula (I):



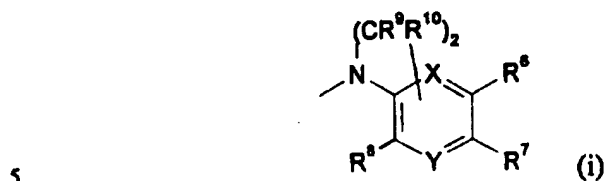
wherein:

R<sup>1</sup> and R<sup>2</sup> groups are each independently hydrogen, C<sub>1-6</sub> alkyl optionally substituted by NR<sup>12</sup>R<sup>13</sup>, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylthio, cyano, nitro, halogen, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, NR<sup>12</sup>R<sup>13</sup>, CONR<sup>12</sup>R<sup>13</sup>, NR<sup>12</sup>COR<sup>13</sup>, S(O)<sub>p</sub>NR<sup>12</sup>R<sup>13</sup>, CHO, OCF<sub>3</sub>, SCF<sub>3</sub>, COR<sup>14</sup>, CH<sub>2</sub>OR<sup>14</sup>, CO<sub>2</sub>R<sup>14</sup> or OR<sup>14</sup> where p is 1 or 2 and R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> are independently hydrogen, C<sub>1-6</sub> alkyl, optionally substituted aryl or optionally substituted arylC<sub>1-6</sub>alkyl, or R<sup>1</sup> and R<sup>2</sup> are N<sup>+</sup>I<sup>-</sup>R<sup>12</sup>R<sup>13</sup>CR<sup>12</sup>R<sup>13</sup>OCOR<sup>14</sup> where R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> are as defined above and I is a counter ion;

n and m are independently 0, 1 or 2;

R<sup>3</sup> is hydrogen or C<sub>1-6</sub> alkyl;

R<sup>4</sup> is a group of formula (i):

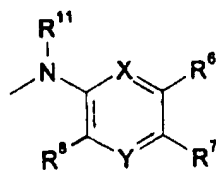


in which:

X and Y are both nitrogen, one is nitrogen and the other is carbon or a CR<sup>5</sup> group or one is a CR<sup>5</sup> group and the other is carbon or a CR<sup>5</sup> group;

- 10 R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> groups are independently hydrogen, C<sub>1-6</sub> alkyl optionally substituted by one or more fluorine atoms, C<sub>2-6</sub> alkenyl, C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkylC<sub>1-6</sub>alkoxy, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyloxy, C<sub>3-6</sub> cycloalkyl-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylthio, C<sub>3-6</sub> cycloalkylthio, C<sub>3-6</sub> cycloalkyl-C<sub>1-6</sub> alkylthio, C<sub>1-6</sub>alkoxy, hydroxy, halogen, nitro, OCF<sub>3</sub>, SCF<sub>3</sub>, SO<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>F, formyl, C<sub>2-6</sub> alkanoyl, cyano, optionally substituted phenyl or thienyl, NR<sup>12</sup>R<sup>13</sup>, CONR<sup>12</sup>R<sup>13</sup> or
- 15 CO<sub>2</sub>R<sup>14</sup> where where R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> are as defined for R<sup>1</sup>; or R<sup>6</sup> and R<sup>7</sup> form part of an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring; R<sup>9</sup> and R<sup>10</sup> are independently hydrogen or C<sub>1-6</sub> alkyl; or R<sup>4</sup> is a group of formula (ii):

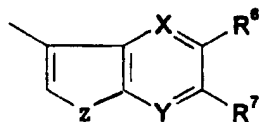
20



(ii)

- 25 in which X and Y are both nitrogen, one is nitrogen and the other is a CR<sup>5</sup> group or X and Y are both CR<sup>5</sup> groups and R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are as defined in formula (I); and R<sup>11</sup> is hydrogen or C<sub>1-6</sub> alkyl, or

R<sup>4</sup> is a group of formula (iii):



5

(iii)

in which R<sup>6</sup>, R<sup>7</sup>, X and Y are as defined in formula (i) and Z is O, S, CH<sub>2</sub> or NR<sup>15</sup> where R<sup>15</sup> is hydrogen or C<sub>1-6</sub> alkyl;

P<sup>1</sup> and P<sup>2</sup> are independently phenyl, aromatic or partially saturated monocyclic or bicyclic heterocyclic rings said heterocyclic rings containing a quaternary nitrogen atom and up to two further heteroatoms selected from nitrogen, oxygen or sulphur;  
10 and

A is a bond, a chain of 1 to 5 atoms optionally substituted by C<sub>1-6</sub> alkyl or A is an optionally substituted phenyl or an optionally substituted 5- to 7-membered heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or  
15 sulphur.

C<sub>1-6</sub> Alkyl groups, whether alone or as part of another group, may be straight chain or branched.

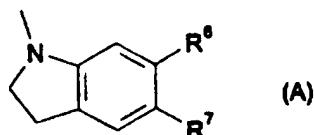
Suitably R<sup>1</sup> and R<sup>2</sup> groups are each independently hydrogen, C<sub>1-6</sub> alkyl optionally substituted by NR<sup>12</sup>R<sup>13</sup>, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkylthio, cyano, nitro, halogen, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, NR<sup>12</sup>R<sup>13</sup>, CONR<sup>12</sup>R<sup>13</sup>, NR<sup>12</sup>COR<sup>13</sup>,  
20 S(O)<sub>p</sub>NR<sup>12</sup>R<sup>13</sup>, CHO, OCF<sub>3</sub>, SCF<sub>3</sub>, COR<sup>14</sup>, CH<sub>2</sub>OR<sup>14</sup>, CO<sub>2</sub>R<sup>14</sup> or OR<sup>14</sup> where p is 1 or 2 and R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> are independently hydrogen, C<sub>1-6</sub> alkyl, optionally substituted aryl or optionally substituted arylC<sub>1-6</sub>alkyl, or R<sup>1</sup> and R<sup>2</sup> are N<sup>+</sup>X<sup>-</sup>-R<sup>12</sup>R<sup>13</sup>CR<sup>12</sup>R<sup>13</sup>OCOR<sup>14</sup> where R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> are as defined above and X is a  
25 counter ion. Examples of suitable aryl groups include phenyl. Examples of suitable arylC<sub>1-6</sub>alkyl groups include benzyl.

Preferably R<sup>1</sup> is hydrogen or methyl.

Preferably R<sup>2</sup> is hydrogen, halogen, methyl, CF<sub>3</sub> or OCF<sub>3</sub>, most preferably R<sup>2</sup> is hydrogen, halogen or methyl.

30 Preferably R<sup>3</sup> is hydrogen.

Preferably  $R^4$  is a group of formula (i). Preferably X and Y form part of a phenyl ring, that is to say one of X or Y is carbon and the other is a CH group or both of X and Y are CH groups. Most preferably  $R^4$  is a group of formula (A):



5

in which  $R^6$  and  $R^7$  are as defined in formula (i).

Suitably  $R^6$  and  $R^7$  groups are independently hydrogen,  $C_{1-6}$  alkyl optionally substituted by one or more fluorine atoms for example  $CF_3$  or  $C_2F_5$ ,  $C_{2-6}$  alkenyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl $C_{1-6}$ alkoxy,  $C_{2-6}$  alkynyl,  $C_{3-6}$  cycloalkyloxy,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkyl,  $C_{1-6}$  alkylthio,  $C_{3-6}$  cycloalkylthio,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkylthio,  $C_{1-6}$ alkoxy, hydroxy, halogen, nitro,  $CF_3$ ,  $C_2F_5$ ,  $OCF_3$ ,  $SCF_3$ ,  $SO_2CF_3$ ,  $SO_2F$ , formyl,  $C_{2-6}$  alkanoyl, cyano, optionally substituted phenyl or thienyl,  $NR^{12}R^{13}$ ,  $CONR^{12}R^{13}$  or  $CO_2R^{14}$  where  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  are as defined for  $R^1$ ; or  $R^6$  and  $R^7$  form part of an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring. Examples of such rings include cyclopentane and dihydrofuran rings.

15

Preferably  $R^6$  is trifluoromethyl or halogen and  $R^7$  is  $C_{1-6}$  alkoxy, in particular methoxy,  $C_{1-6}$ alkylthio, in particular methylthio or  $C_{1-6}$  alkyl in particular methyl.

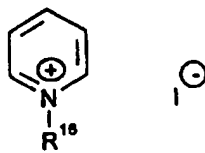
20

Suitably n and m are independently 0, 1 or 2. Preferably n is 0 or 1.

Suitably  $P^1$  and  $P^2$  are independently phenyl, aromatic or partially saturated monocyclic or bicyclic heterocyclic rings containing a quaternary nitrogen atom and up to two further heteroatoms selected from nitrogen, oxygen or sulphur. Preferably

$P^1$  and/or  $P^2$  is a quaternary group of formula (B)

25



(B)

where R<sup>16</sup> is C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, oxygen, NR<sup>17</sup>R<sup>18</sup>, NHCONR<sup>17</sup>R<sup>18</sup>,  
 NHCOR<sup>19</sup>, CR<sup>17</sup>R<sup>18</sup>OCOR<sup>19</sup>, OCR<sup>17</sup>R<sup>18</sup>OCOR<sup>19</sup>, CR<sup>17</sup>R<sup>18</sup>OCONR<sup>17</sup>R<sup>18</sup>, or  
 OCR<sup>17</sup>R<sup>18</sup>OCONR<sup>17</sup>R<sup>18</sup> where R<sup>17</sup>, R<sup>18</sup> and R<sup>19</sup> are independently hydrogen,  
 5 C<sub>1-20</sub> alkyl, optionally substituted aryl or optionally substituted arylC<sub>1-6</sub>alkyl  
 and I<sup>-</sup> is a counter ion.

More preferably P<sup>1</sup> is a group of formula (A) where R<sup>16</sup> is  
 CR<sup>17</sup>R<sup>18</sup>OCOR<sup>19</sup>. Most preferably R<sup>17</sup> and R<sup>18</sup> are both hydrogen. Preferred  
 counter ions include halogen such as chloro or iodo.

10 P<sup>2</sup> is preferably phenyl or pyridyl.

The urea moiety can be attached to a carbon or any available nitrogen atom of  
 the ring P<sup>2</sup>, preferably it is attached to a carbon atom. Suitable moieties when the ring  
 P<sup>2</sup> is a 5-membered aromatic heterocyclic rings include isothiazolyl, isoxazolyl,  
 thiadiazolyl, oxadiazolyl and triazolyl. Suitable moieties when the ring P<sup>2</sup> is a 6-  
 15 membered aromatic heterocyclic rings include, for example, pyridyl, pyrimidyl or  
 pyrazinyl. Optional substituents for P<sup>1</sup> and P<sup>2</sup> groups include those groups R<sup>1</sup> and R<sup>2</sup>  
 listed above.

Suitably A is a bond or a chain of 1 to 5 atoms optionally substituted by  
 C<sub>1-6</sub> alkyl. Examples of such chains include (CH<sub>2</sub>)<sub>p</sub>E or E(CH<sub>2</sub>)<sub>p</sub> where p is 1 to 4  
 20 and E is CO, O, S(O)<sub>x</sub> where x is 0 to 2 or A is NR, CONR, NRCO, NRCONR, CO,  
 CH(OH), C<sub>1-6</sub>alkyl, CH=CH, CH=CF, CF=CF, O, S(O)<sub>x</sub> where x is 1 or 2, NR, or  
 NRSO<sub>2</sub> where R is hydrogen or C<sub>1-6</sub> alkyl. Preferably A is a bond or a group CH<sub>2</sub>O,  
 OCH<sub>2</sub>, or O. Most preferably A is a bond or O.

Suitably A is an optionally substituted phenyl group or an optionally  
 25 substituted 5- or 6-membered heterocyclic ring containing up to three heteroatoms  
 selected from nitrogen, oxygen or sulphur. Preferably A is thiazolyl, isothiazolyl,  
 oxazolyl, isoxazolyl, thiadiazolyl, triazolyl, pyridyl, pyrimidyl or pyrazinyl. Most  
 preferably A is thiazolyl. Optional substituents when A is a phenyl or a heterocyclic  
 group include those groups R<sup>1</sup> and R<sup>2</sup> listed above

30 Particular compounds of the invention include:

5-Methoxy-6-trifluoromethyl-1-[3-fluoro-5-[1-(acetyloxy)methyl-pyridinium-3-  
 yl]phenylcarbamoyl]indoline chloride,

5-Methoxy-6-trifluoromethyl-1-[3-fluoro-4-methyl-5-[1-(acetyloxy)methylpyridinium-3-yl]phenylcarbamoyl]indoline chloride,

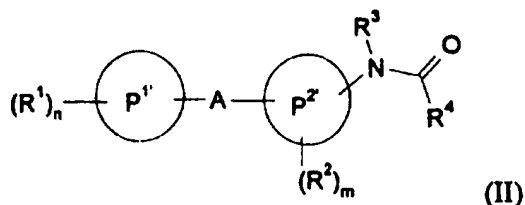
5,6-Dichloro-1-[6-[1-(acetyloxy)methyl-2-methylpyridinium-3-yl-oxy] pyridin-3-ylcarbamoyl]indoline, and

- 5 5-Methoxy-6-trifluoromethyl-1-[3,4-difluoro-5-[1-(acetyloxymethyl)pyridinium-3-yl]phenylcarbamoyl] indoline chloride.

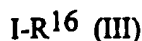
Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises

- (a) for compounds of formula (I) where  $P^1$  and/or  $P^2$  are a group of formula (A) or (B) reaction of a compound of formula (II):



in which A,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , n and m are as defined in formula (I) and  $P^1$  and  $P^2$  are independently phenyl, aromatic or partially saturated monocyclic or bicyclic heterocyclic rings containing up to three heteroatoms selected from nitrogen, oxygen or sulphur, with a compound of formula (III):



in which  $R^{16}$  is as defined in formula (I) and I is a leaving group.



The reaction of compounds (II) and (III) is preferably carried out in an inert solvent such as acetonitrile in the presence of a boron coupling reagent such as tetraphenylboron. Preferably I is a leaving group such as halogen.

Those skilled in the art will appreciate that it may be necessary to protect  
5 certain reactive groups in compounds of formulae (II) and (III) during the coupling reaction. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

Compounds of formula (I) and their pharmaceutically acceptable salts have  
10 5HT<sub>2B/2C</sub> receptor antagonist activity and are believed to be of potential use for the treatment or prophylaxis of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also  
15 disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

Thus the invention also provides a compound of formula (I) for use as a  
20 therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I).

25 In another aspect, the invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment or prophylaxis of the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) and a pharmaceutically acceptable carrier.

30 A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form

of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and  
5 may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry  
10 product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a  
15 compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic,  
20 preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can  
25 be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of  
30 administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight

of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and  
5 such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

10

**Example 1****5-Methoxy-6-trifluoromethyl-1-[3-fluoro-5-[1-(acetyloxy)methyl-pyridinium-3-yl]phenylcarbamoyl]indoline chloride (E1)**

5 To a solution of 5-methoxy-6-trifluoromethyl-1-[3-fluoro-5-(pyridin-3-yl)phenylcarbamoyl]indoline (0.5g, 1.16 mmol) in acetonitrile (20 ml) was added sodium tetraphenylboron (0.48g, 1.40 mmol) followed by bromomethyl acetate (0.14 ml, 1.43 mmol). The resulting mixture was heated at reflux under argon for 4 h, then cooled to room temperature, and filtered through a kieselgühr pad. The filtrate was  
10 concentrated to give the pyridinium tetraphenylborate salt as a yellow solid which was taken-up in acetonitrile/2-propanol (20 ml; 1:1 v/v) and passed through an ion-exchange column (2 x 10 cm of Dowex 1x2 chloride, 50-100 mesh) at ca. 1 ml/min. The eluant was concentrated, and the resulting solid was triturated with diethyl ether to give after drying the title compound (E1) as a yellow solid (0.63g, 100%) m.p. 145-  
15 150°C.

<sup>1</sup>H NMR (400 MHz; DMSO) δ: 2.18 (3H, s), 3.29 (2H, t, J=8Hz), 3.85 (3H, s), 4.27 (2H, t, J=8Hz), 6.50 (2H, s), 7.24 (1H, s), 7.44 (1H, m, J=10Hz), 7.72 (1H, m, J=11Hz), 8.09 (1H, s), 8.14 (1H, s), 8.34 (1H, dd, J=11Hz, 7Hz), 8.99 (1H, d, J=10Hz), 9.23 (2H, m), 9.59 (1H, s).  
20

Mass spectrum (FAB) 504 (M<sup>+</sup>).

**Example 2**

25 **5-Methoxy-6-trifluoromethyl-1-[3-fluoro-4-methyl-5-[1-(acetyloxy)methylpyridinium-3-yl]phenylcarbamoyl]indoline chloride (E2)**

5-Methoxy-6-trifluoromethyl-1-[3-fluoro-4-methyl-5-(pyridin-3-yl)phenyl  
carbamoyl]indoline (0.195g, 0.44 mmol) was converted to the title compound (E2)  
30 according to the method of Example 1 to give a yellow solid (0.23g, 95%) m.p. 212-4°C.

<sup>1</sup>H NMR (250 MHz; DMSO) δ: 2.12 (3H, m), 2.17 (3H, s), 3.28 (2H, t, J=8Hz), 3.84 (3H, s), 4.22 (2H, t, J=8Hz), 6.49 (2H, s), 7.22 (1H, s), 7.60-7.70 (2H, m), 8.10 (1H, s), 8.36 (1H, dd, J=8Hz, 7Hz), 8.82 (1H, d, J=9Hz), 9.11 (1H, s), 9.28 (1H, d, J=5Hz), 9.49 (1H, s).

5

Mass spectrum (FAB) 518 (M<sup>+</sup>).

### Example 3

**5,6-Dichloro-1-[6-[1-(acetyloxy)methyl-2-methylpyridinium-3-yl-oxy] pyridin-3-ylcarbamoyl]indoline chloride (E3)**

10

5,6-Dichloro-1-[6-(2-methylpyridin-3-yloxy)pyridin-3-ylcarbamoyl]indoline (0.25g, 0.6 mmol) was treated with bromomethyl acetate and sodium tetraphenylboron at reflux in acetonitrile (15 ml) for 10 h according to the procedure described in Example 1 to give the title compound (E3) (0.26g, 80%) m.p. 125-135°C which contained approximately 15% starting material as an off-white solid.

15

<sup>1</sup>H NMR (200 MHz; DMSO) δ: 2.17 (3H, s), 2.79 (3H, s), 3.20 (2H, t, J=8Hz), 4.22 (2H, t, J=8Hz), 6.53 (2H, s), 7.32 (1H, d, J=9Hz), 7.49 (1H, s), 8.02 (1H, s), 8.08 (1H, dd, J=8Hz, 6Hz), 8.20 (1H, dd, J=9Hz, 3Hz), 8.38 (1H, d, J=3Hz), 8.56 (1H, d, J=8Hz), 9.06 (1H, d, J=6Hz), 9.12 (1H, s).

20

### Example 4

**5-Methoxy-6-trifluoromethyl-1-[3,4-difluoro-5-[1-(acetyloxymethyl)pyridinium-3-yl]phenylcarbamoyl] indoline chloride (E4)**

25

5-Methoxy-6-trifluoromethyl-1-[3,4-difluoro-5-(pyridin-3-yl)phenylcarbamoyl]indoline (0.30g, 0.67 mmol) was converted into the title compound (E4) according to the method of Example 1. The tetraphenylborate salt was stirred with Dowex 1x8-200 ion-exchange resin in 1:1 acetonitrile/2-propanol (25 ml) for 24 h. The resin was then filtered off and the filtrate evaporated to give the title compound (0.35g, 94%), mp 201-2°C.

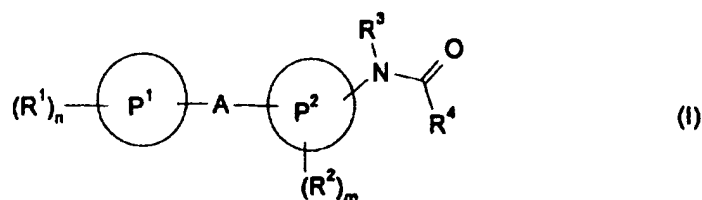
30

<sup>1</sup>H NMR (250 MHz; D<sub>6</sub>DMSO) δ: 2.17 (3H, s), 3.29 (2H, t, J=8Hz), 3.84 (3H, s), 4.25 (2H, t, J=8Hz), 6.51 (2H, s), 7.23 (1H, s), 7.89 (2H, m), 8.12 (1H, s), 8.39 (1H, t, J=7Hz), 8.96 (1H, d, J=7Hz), 9.27 (1H, s), 9.32 (1H, d, J=7Hz), 9.52 (1H, s).

5 Mass Spectrum (FAB) 522 (M<sup>+</sup>).

## Claims

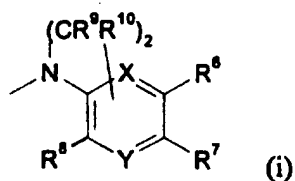
1. A compound of formula (I):



5

wherein:

- $R^1$  and  $R^2$  groups are each independently hydrogen,  $C_{1-6}$  alkyl optionally substituted by  $NR^{12}R^{13}$ ,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{1-6}$  alkylthio, cyano, nitro, halogen,  $CF_3$ ,  $C_2F_5$ ,  $NR^{12}R^{13}$ ,  $CONR^{12}R^{13}$ ,  $NR^{12}COR^{13}$ ,  $S(O)_pNR^{12}R^{13}$ ,  $CHO$ ,  $OCF_3$ ,  $SCF_3$ ,  $COR^{14}$ ,  $CH_2OR^{14}$ ,  $CO_2R^{14}$  or  $OR^{14}$  where  $p$  is 1 or 2 and  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  are independently hydrogen,  $C_{1-6}$  alkyl, optionally substituted aryl or optionally substituted aryl $C_{1-6}$ alkyl, or  $R^1$  and  $R^2$  are  $N^+I^-R^{12}R^{13}CR^{12}R^{13}OCOR^{14}$  where  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  are as defined above and  $I$  is a counter ion;
- $n$  and  $m$  are independently 0, 1 or 2;
- $R^3$  is hydrogen or  $C_{1-6}$  alkyl;
- $R^4$  is a group of formula (i):



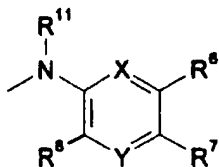
20 in which:

- $X$  and  $Y$  are both nitrogen, one is nitrogen and the other is carbon or a  $CR^5$  group or one is a  $CR^5$  group and the other is carbon or a  $CR^5$  group;
- $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  groups are independently hydrogen,  $C_{1-6}$  alkyl optionally substituted by one or more fluorine atoms,  $C_{2-6}$  alkenyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl $C_{1-6}$ alkoxy,  $C_{2-6}$  alkynyl,  $C_{3-6}$  cycloalkyloxy,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkyl,  $C_{1-6}$  alkylthio,  $C_{3-6}$  cycloalkylthio,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkylthio,

C<sub>1-6</sub>alkoxy, hydroxy, halogen, nitro, OCF<sub>3</sub>, SCF<sub>3</sub>, SO<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>F, formyl, C<sub>2-6</sub>alkanoyl, cyano, optionally substituted phenyl or thienyl, NR<sup>12</sup>R<sup>13</sup>, CONR<sup>12</sup>R<sup>13</sup> or CO<sub>2</sub>R<sup>14</sup> where where R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> are as defined for R<sup>1</sup>; or R<sup>6</sup> and R<sup>7</sup> form part of an optionally substituted 5- or 6-membered carbocyclic or heterocyclic ring;

5 R<sup>9</sup> and R<sup>10</sup> are independently hydrogen or C<sub>1-6</sub> alkyl; or

R<sup>4</sup> is a group of formula (ii):

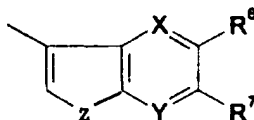


10

(ii)

in which X and Y are both nitrogen, one is nitrogen and the other is a CR<sup>5</sup> group or X and Y are both CR<sup>5</sup> groups and R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are as defined in formula (I); and R<sup>11</sup> is hydrogen or C<sub>1-6</sub> alkyl, or

15 R<sup>4</sup> is a group of formula (iii):



(iii)

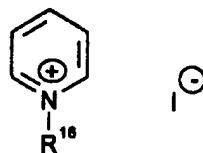
20 in which R<sup>6</sup>, R<sup>7</sup>, X and Y are as defined in formula (i) and Z is O, S, CH<sub>2</sub> or NR<sup>15</sup> where R<sup>15</sup> is hydrogen or C<sub>1-6</sub> alkyl;

P<sup>1</sup> and P<sup>2</sup> are independently phenyl, aromatic or partially saturated monocyclic or bicyclic heterocyclic rings containing a quaternary nitrogen atom and up to two further heteroatoms selected from nitrogen, oxygen or sulphur; and

25 A is a bond, a chain of 1 to 5 atoms optionally substituted by C<sub>1-6</sub> alkyl or A is an optionally substituted phenyl or an optionally substituted 5- to 7-membered heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur.



2. A compound according to claim 1 where P<sup>1</sup> is a group of formula (B):



(B)

- 5 where R<sup>16</sup> is C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, oxygen, NR<sup>17</sup>R<sup>18</sup>, NHCONR<sup>17</sup>R<sup>18</sup>, NHCOR<sup>19</sup>, CR<sup>17</sup>R<sup>18</sup>OCOR<sup>19</sup>, OCR<sup>17</sup>R<sup>18</sup>OCOR<sup>19</sup>, CR<sup>17</sup>R<sup>18</sup>OCONR<sup>17</sup>R<sup>18</sup>, or OCR<sup>17</sup>R<sup>18</sup>OCONR<sup>17</sup>R<sup>18</sup> where R<sup>17</sup>, R<sup>18</sup> and R<sup>19</sup> are independently hydrogen, C<sub>1-20</sub> alkyl, optionally substituted aryl or optionally substituted arylC<sub>1-6</sub>alkyl and I<sup>-</sup> is a counter ion.

10

3. A compound according to claim 1 or 2 where P<sup>2</sup> is phenyl or pyridyl.
4. A compound according to any one of claims 1 to 3 where R<sup>4</sup> is a group of formula (A).

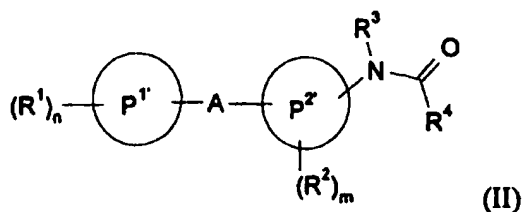
15

5. A compound according to any one of claims 1 to 4 which is:
- 5-Methoxy-6-trifluoromethyl-1-[3-fluoro-5-[1-(acetyloxy)methyl-pyridinium-3-yl]phenylcarbamoyl]indoline chloride,
- 5-Methoxy-6-trifluoromethyl-1-[3-fluoro-4-methyl-5-[1-(acetyloxy)methylpyridinium-3-yl]phenylcarbamoyl]indoline chloride,
- 20 5,6-Dichloro-1-[6-[1-(acetyloxy)methyl-2-methylpyridinium-3-yl-oxy] pyridin-3-ylcarbamoyl]indoline, or
- 5-Methoxy-6-trifluoromethyl-1-[3,4-difluoro-5-[1-(acetyloxymethyl)pyridinium-3-yl]phenylcarbamoyl] indoline chloride.

25

6. A compound according to any one of claims 1 to 5 for use in therapy.
7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 and a pharmaceutically acceptable excipient.

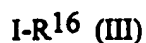
8. A process for preparing a compound of Claim 1 in which R is substituted alkyl which comprises reacting a compound of a compound of formula (II):



5

in which A,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , n and m are as defined in Claim 1 and  $P^{1'}$  and  $P^{2'}$  are independently phenyl, aromatic or partially saturated monocyclic or bicyclic heterocyclic rings containing up to three heteroatoms selected from nitrogen, oxygen or sulphur, with a compound of formula (III):

10



in which  $R^{16}$  is as defined in Claim 1 and I is such that  $I^-$  is a leaving group.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/01611

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 C07D401/12 A61K31/44 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 22871 A (SMITHKLINE BEECHAM PLC ;FORBES IAN THOMSON (GB); MARTIN ROGER THOM) 13 October 1994 see the whole document ---	1,3,6,7
X	WO 94 04533 A (SMITHKLINE BEECHAM PLC ;FORBES IAN THOMSON (GB); MARTIN ROGER THOM) 3 March 1994 see the whole document ---	1,3,4,6, 7
X	WO 92 05170 A (BEECHAM GROUP PLC) 2 April 1992 see the whole document ---	1,3,6,7
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*A\* document member of the same patent family

Date of the actual completion of the international search

15 July 1997

Date of mailing of the international search report

29.07.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

De Jong, B

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/01611

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE Beilstein XP002001373 BRN=2955290 & DE-A-2955290	1,3
X	--- DATABASE CROSSFIRE Beilstein XP002001374 BRN=3419367 & JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 79, 1957, DC US, pages 1236-1242, BEAVER ET AL.:	1,3
X	--- DATABASE CROSSFIRE Beilstein XP002001375 BRN=2138496 & TETRAHEDRON LETTERS, 1970, OXFORD GB, page 4905 GRUPON ET AL.:	1,3
P,X	--- WO 96 23783 A (SMITHKLINE BEECHAM PLC ;GASTER LARAMIE MARY (GB); WYMAN PAUL ADRIA) 8 August 1996 see the whole document -----	1-8

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 97/01611

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
Claims 1 and 3 are so broad that a complete search was not possible for economical reasons. Only a few examples of novelty destroying documents have been cited in the search report.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/01611

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9422871 A	13-10-94	EP 0691973 A JP 8508275 T	17-01-96 03-09-96
WO 9404533 A	03-03-94	AU 4704693 A CA 2142721 A CN 1086819 A EP 0656003 A JP 8500580 T NZ 254785 A SI 9300438 A ZA 9306050 A	15-03-94 03-03-94 18-05-94 07-06-95 23-01-96 26-09-95 31-03-94 20-02-95
WO 9205170 A	02-04-92	AU 642041 B AU 8503891 A CA 2091246 A EP 0550507 A JP 6500551 T US 5328922 A	07-10-93 15-04-92 14-03-92 14-07-93 20-01-94 12-07-94
WO 9623783 A	08-08-96	AU 4664696 A	21-08-96

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**